BRAIN
SCIENTIFIC COMMENTARY

Side-effects are often a curse. Can they also be a blessing?

This scientific commentary refers to 'How side effects can improve treatment efficacy: a randomized trial' by Schenk *et al*. (https://doi.org/10.1093/brain/awae132).

The therapeutic effect of medicines is determined by more than their pharmacological properties. Factors such as the colour of a tablet, its taste and even its price have been found to significantly influence efficacy.[1,2] This insight has sparked optimism about the potential to enhance drug effects by tweaking these and other features to optimize therapeutic outcomes. In this issue of *Brain*, Schenk and colleagues[3] add a somewhat counter-intuitive factor to the list of features that could be targeted to boost the efficacy of a drug: side effects.

In an experimental study combining behavioural and neuroimaging measures, 77 healthy volunteers were told that they had a 50% chance of receiving a nasal spray containing either fentanyl or placebo; they would then be exposed to noxious thermal stimuli and would be asked to rate the intensity of the resulting pain. In fact, the volunteers were given a placebo on every trial, but the placebo was either (i) administered alone (control condition); (ii) administered in combination with a reduction in the temperature of the thermal stimuli to induce the perception of analgesia (inert placebo); or (iii) administered in combination with a reduction in the temperature of the thermal stimuli and experimentally induced side effects (a burning sensation in the nose caused by the addition of capsaicin to the nasal spray) (active placebo).

During the first test session, participants reported less pain in both placebo conditions—active and inert—compared to the control condition. However, the analgesic effect was slightly but significantly more pronounced when the placebo was accompanied by side effects (Fig. 1A, session 1). Moreover, the active placebo led to stronger engagement of the descending pain modulatory network and stronger coupling between two key components of this network [the rostral anterior cingulate cortex (rACC) and periaqueductal grey (PAG)]. Crucially, this greater analgesic effect was dependent on participants believing that the occurrence of side effects indicates a more potent treatment, with this belief leading to more positive treatment expectations which in turn resulted in increased analgesia (Fig. 1B). These findings provide new insights into the (neurobiological) mechanisms underlying the known effects of active placebos (see, for instance Rebstock *et al*.[4] and Jenson *et al*.[5]).

The ability of perceived side effects to influence reported drug efficacy is a well-known challenge for the design of placebo-controlled clinical trials. Side effects can signal to patients that they are receiving the active drug and can inadvertently unblind a trial long before it is completed. This is particularly problematic in trial designs where patients have an equal chance of receiving the active drug or a placebo. In such scenarios, identifying the active drug is often straightforward: the treatment with the stronger (or any) side effects is more likely to be the active drug. Once the trial has been unblinded in this way, expectancy effects can enhance the treatment effect beyond the biological effect, leading to overestimates of treatment efficacy compared to placebo.

In clinical practice, inferring treatment potency is far more difficult. It may be that none of the prescribed drugs are effective, and there is no comparison with an inert substance to help identify the more effective treatment. However, the findings of Schenk and colleagues[3] provide valuable insights into the role of side effects in symptom perception and treatment outcomes in clinical scenarios. They suggest that during treatment, our assessment of drug effects may be guided by simple heuristics (e.g. 'more potent treatments have more side effects'; Fig. 1B), which may not always hold true but are often a reasonable first approximation. Remarkably, Schenk and colleagues[3] found that the latter belief was strong enough to resurface even after participants had been debriefed about the active placebo manipulation. While the analgesia-enhancing effect of side effects disappeared immediately after the debriefing prior to the second session ('No Expectation' group; Fig. 1A, session 2), it re-emerged in a follow-up session conducted about a week later (Fig. 1A, session 3). This suggests that side effects and treatment effects are intricately linked, often through their co-occurrence; side effects can thus act as a conditioned cue, the importance of which cannot easily be overridden by verbal information.

Whether and how the current findings can be translated to clinical practice remains to be determined. Side effects are a key concern in any treatment context, and they must not be ignored in the hope of enhancing treatment effectiveness. Instead, the authors suggest actively supporting patients' perception that side effects are a sign that the body is responding to the treatment in the desired way. This 'positive framing' of side effects has been shown not only to reduce the burden of side effects,[6,7] but also to enhance the desired treatment outcomes.[8] This approach may be particularly promising in cases where there is a significant delay between the onset of a side effect and the desired therapeutic effect, which makes it more difficult for the patient to establish a causal connection between the two events. In their study, Schenk

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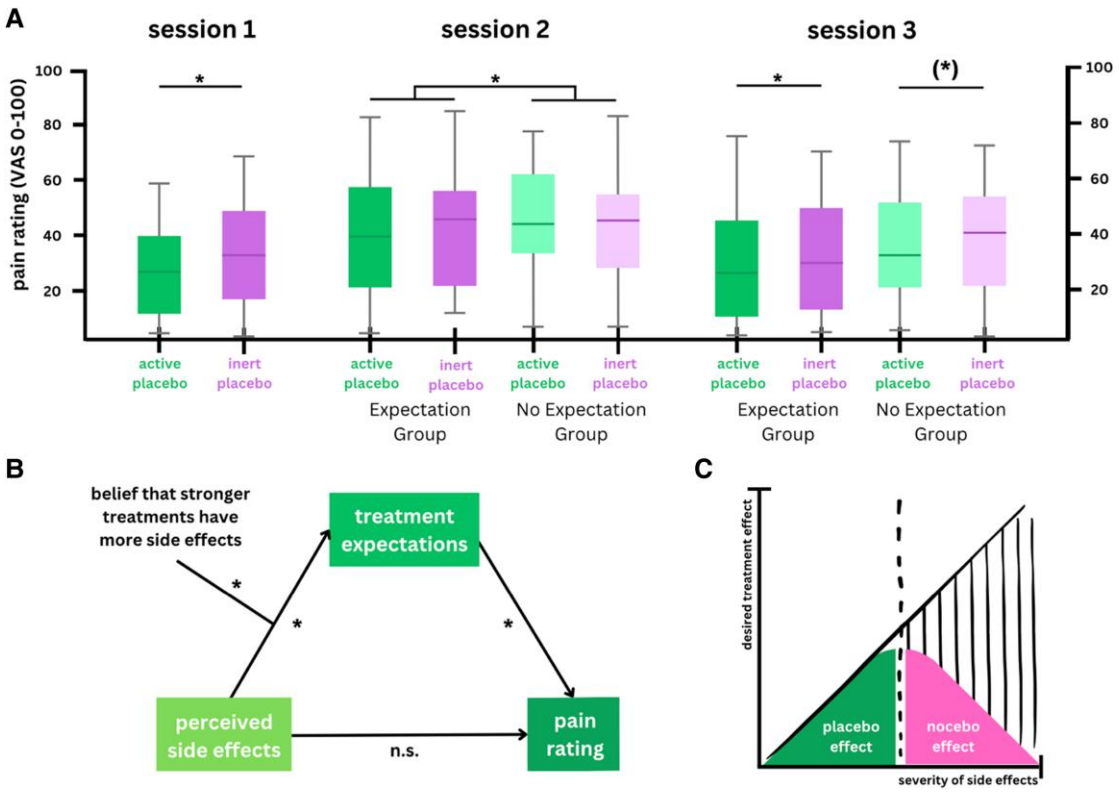

Figure 1 Overview of the study by Schenk *et al.*[3] (A and B) and implications (C). (**A**) Healthy volunteers were informed that they would receive a nasal spray containing either fentanyl or a placebo (50:50 probability) before being exposed to noxious thermal stimuli and being asked to rate the intensity of pain on a visual analogue scale (VAS). In fact, all participants were given a placebo in each of the three test runs in session 1. In one run, the placebo was combined with a reduction in the temperature of the thermal stimuli to induce the perception of analgesia (inert placebo). In another run, the placebo was combined with the temperature reduction plus experimentally induced side effects (a burning sensation in the nose caused by the addition of capsaicin to the nasal spray) (active placebo). These two placebo runs were preceded by a control condition, in which the placebo was given without the temperature manipulation or side effects (results not shown). The active placebo induced a stronger analgesic effect than the inert placebo (session 1). Before the second session, half of the participants were debriefed about the active placebo manipulation (No Expectation group). Whereas the Expectation group continued to show stronger pain reduction with the active placebo, this effect was no longer present in the No Expectation group (session 2). Notably, however, it re-emerged as a marginally significant effect in a follow-up session approximately a week later (session 3). (**B**) The belief that more potent treatments have more side effects (rated on a 5-point scale) mediated the effect of perceived side effects on treatment expectations, with changes in expectations leading to a reduction in pain ratings. (**C**) While the findings of Schenk *et al.*[3] might suggest a linear relationship between the severity of side effects and the desired treatment outcome (shown in vertical stripes), this influence is likely to be constrained by other factors (e.g. an increase in perceived threat, the burden imposed by stronger side effects and a decrease in adherence). As a result, the treatment-enhancing placebo effect (shown in green) may level off or even turn into a nocebo effect (shown in pink) at a certain inflection point. The figure was created by the authors using the free version of Canva.

and colleagues[3] provided concrete information about the expected onset of the effects ('takes effect in as little as 3 min') to allow for precise temporal expectations. More controversially, it could be debated whether—similar to the use of active placebos—mild and benign side effects could deliberately be introduced and coupled with a treatment to try to improve therapeutic outcomes. This approach has yet to be systematically tested in clinical applications, due in part to the substantial ethical implications.

To be able to use side effects as a strategy to enhance treatment outcomes in a safe and ethical manner, it is essential to understand their limitations. First, whereas mild side effects may be compatible with the notion that they are also indicative of a desired effect on the body, this is not likely to be the case for more severe side effects, especially those that cause significant discomfort. The relationship between perceived side effects and symptom relief may therefore resemble an inverted U-shaped function rather than a linear increase (Fig. 1C) and maximum benefit (also through better adherence) may only be achieved when side effects are perceived without eliciting a threat response. Second, this inflection point is likely to vary between different side effects and side effect intensities, as well as based on individual differences in perception, expectations, and past experience. For example, a mild tingling sensation in the extremities may be perceived as harmless by some and as worrying by others. Third, the framing of side effects must respect ethical standards and should not jeopardize patient autonomy and the patient–practitioner relationship. It is therefore crucial for patients and practitioners to engage in joint decision-making about the use of positive framing as part of treatment.[9]

In conclusion, Schenk and colleagues[3] convincingly demonstrate the potential for side effects, and our interpretation of their meaning, to influence treatment outcomes, albeit so far only in an experimental setting in healthy individuals. The struggle faced by many patients with debilitating side effects, and the ability of side effects to limit the use of highly effective drugs, leave no doubt that they are often perceived as a curse. Whether (mild and benign) side effects can also be a blessing, will depend on whether we can decipher the role they play in the therapeutic process.

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Competing interests

The authors report no competing interests.

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